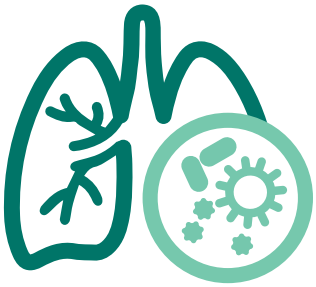
DRINKING AND TUBERCULOSIS



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IARD Health Reviews offer a referenced overview of recent peer-reviewed, published research on the relationship between alcohol consumption and health outcomes. The Reviews report the findings of the referenced studies and are not intended to provide advice or recommendations. They are not necessarily intended to be exhaustive representations of all scientific research on a given subject and, as research is constantly evolving, they may not include the most recent findings. These materials do not necessarily reflect the views of IARD or its member companies. The reviews report the findings of the referenced studies and are not intended to advise individuals about their drinking. People with specific questions about their drinking are encouraged to consult a healthcare professional; together, they can determine what is best based on individual risk factors, including family history, genetics, and lifestyle. For some people, the better choice may be to not drink at all. IARD Health Reviews should be read in their entirety and not misrepresented or taken out of context.

There is a glossary of key terms used in this chapter on **page 22**.

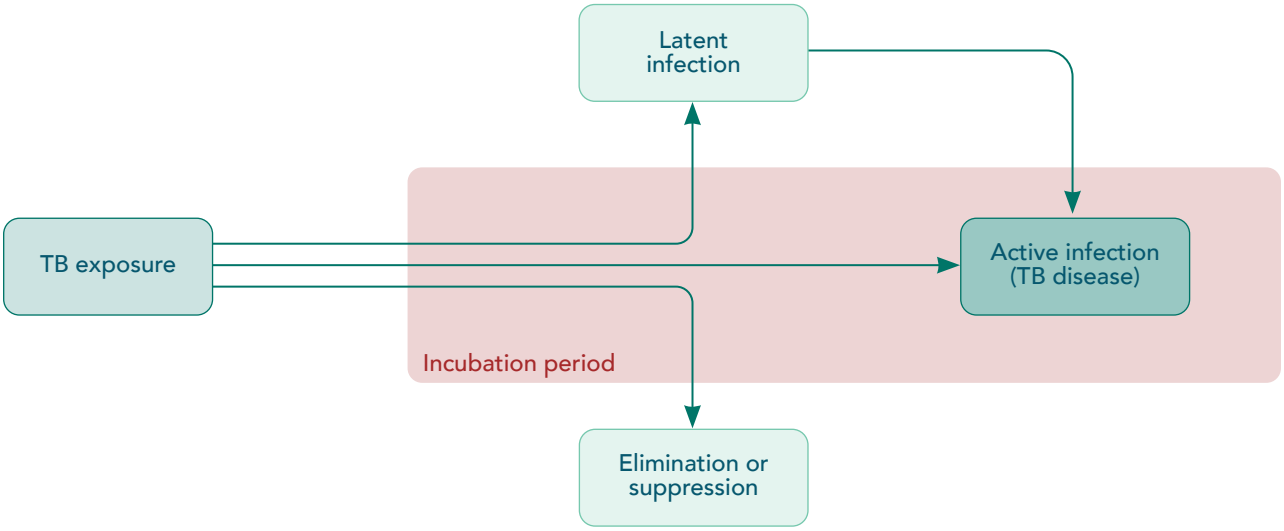
Last literature review: **September 2022**

Tuberculosis (TB) background

Tuberculosis (TB) infection is caused by the bacteria *Mycobacterium tuberculosis* and primarily affects the lungs, but can spread to other organs. Individuals are classified as having either latent or active TB infection [1, 2].

Individuals with a latent infection do not have symptoms and are not infectious, but they may carry a small amount of inactive TB bacteria in their lungs [1]. Although approximately 90% of infections are resolved (suppressed or eliminated) by a healthy *immune response*, 5% to 10% of latent infections progress to active TB infection at some point during a person's lifetime [1, 3]. Individuals with active TB infection (also described as active TB disease) have symptoms, can spread the bacteria to other people when they cough or sneeze, and require medical treatment to prevent serious illness and death [1]. Figure 1 describes the natural course of TB from exposure to the bacteria to the disease state.

Figure 1. Natural course of TB infection and disease progression



Notes.
- Not all persons exposed to TB will incubate the bacteria and become infected
- Individuals with a strong immune system are able to eliminate or suppress the infectious organism

Risk of TB disease depends on exposure to the bacteria, the strength or weakness of an individual's immune system, and the biological traits of the bacterium. Therefore, the prevalence of latent TB infection in a population will influence the absolute risk of TB. Among populations with a low prevalence of latent TB, TB morbidity and mortality may remain low even where a sizable population is susceptible (that is, likely to be harmed due to risk factors for a weakened immune system) [3].

In 2019, 8.5 million newly diagnosed TB cases (incidence) and 1.2 million TB deaths were reported worldwide, and TB was the 13th leading cause of death globally [4]. *See the* Background chapter *of this Health Review for an overview of TB and other infectious diseases.*

TB incidence and mortality rates are higher among men than women globally, and there is a large disparity in the distribution of disease between high- and low-income countries. The TB mortality rate is 113 times higher for women and 97 times higher for men in low-income countries than for women and men in high-income countries (see Table 1) [4].

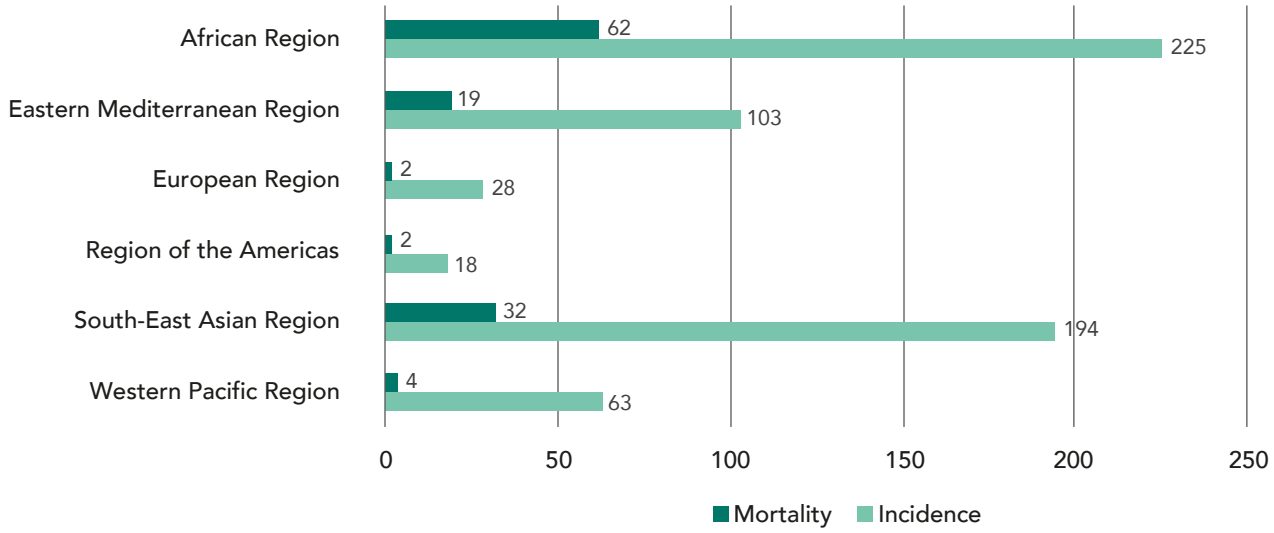
Table 1. 2019 tuberculosis incidence and mortality rates per 100,000 by World Bank income levels, grouped by sex

Rates per 100,000	TB incidence		TB mortality	
	Women	Men	Women	Men
Global	94.9	119.6	10.1	19.7
Low Income	205.5	270.4	50.4	95.5
Lower-Middle Income	164.4	211.1	22.5	43.2
Upper-Middle Income	40.5	60.9	1.8	4.6
High Income	7.7	10.9	0.4	1.0
Low-to-high Ratio	26.6	24.7	113.4	97.7

Source: Institute for Health Metrics and Evaluation, Global Burden of Disease 2019 [4]

When grouped by World Health Organization (WHO) regions, TB incidence and mortality rates are highest in the African Region and lowest in the Regions of the Americas [4].

Figure 2. 2019 tuberculosis incidence and mortality rates per 100,000 by WHO regions



Source: Institute for Health Metrics and Evaluation, Global Burden of Disease 2019 [4]

The WHO's Global Tuberculosis Report 2022 reported a drop in the number of newly diagnosed TB cases reported in 2020 and 2021, compared to 2019, which was attributed to the disruption in initiation or continuity of health care services during the COVID-19 pandemic. Disruption in TB diagnosis and treatment during the pandemic likely contributed to greater community transmission of TB and the first increase in TB mortality rates since 2005 [2].

According to the WHO, 87% of new TB diagnoses come from 30 high TB burden countries and just eight of these countries account for the majority (67%) of the global total (India, Indonesia, China, the Philippines, Pakistan, Nigeria, Bangladesh,

and the Democratic Republic of Congo). Twenty-nine of the 30 high TB burden countries are also listed as having high burden of TB and human immunodeficiency virus (HIV) co-infected cases, or high burden of drug-resistant TB cases, or both (see Appendix 1: Figure A1 for WHO lists of high burden countries) [2].

RISK FACTORS FOR TB

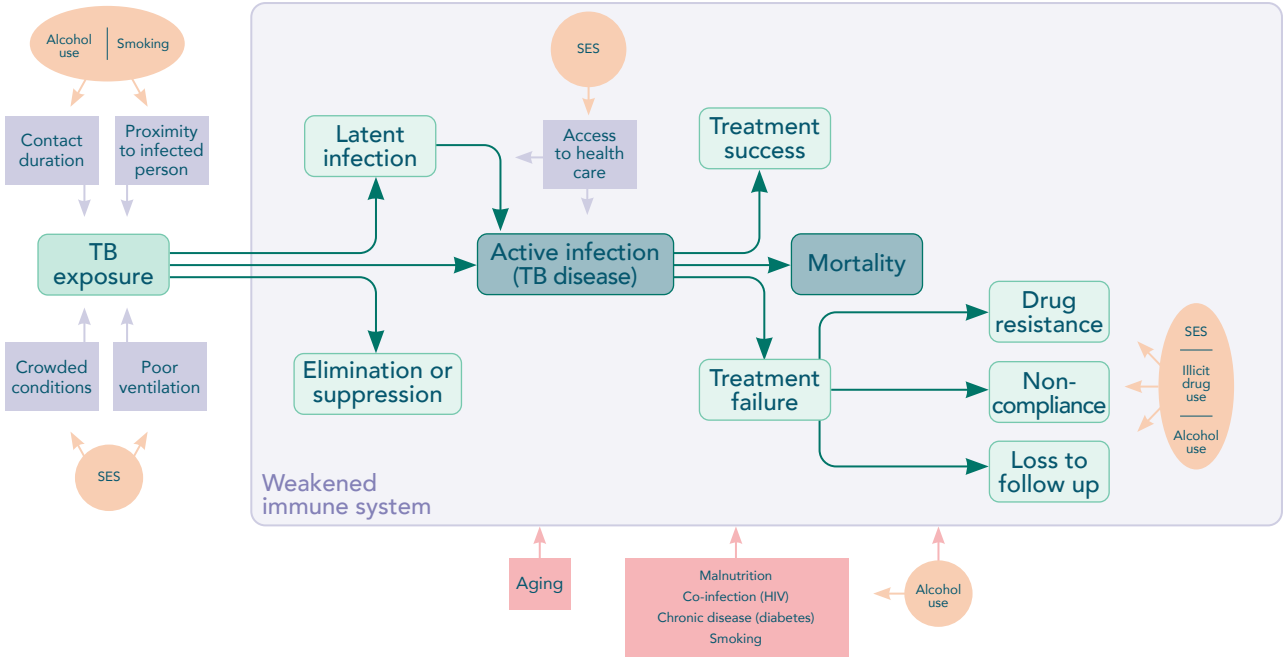
Risk of TB infection and disease is associated with direct and indirect risk factors through multiple mechanisms (see Figure 3).

- **Direct**: A weakened immune system increases susceptibility to TB infection and increases the risk of disease progression and severity [3]. Individual risk factors that may contribute to a compromised immune system include aging, alcohol consumption, co-occurring chronic diseases (such as, diabetes and liver disease) or other infectious diseases (such as, HIV infection), malnutrition, and smoking [3, 5-8].

  In addition, certain behavioral, social, or environmental factors increase the likelihood of TB exposure, infection, or disease progression. These factors include proximity to an infected person, duration of contact with an infected person, crowded living or working conditions, poor ventilation, and lack of access to healthcare services [6].

- **Indirect**: Individual risk factors can indirectly increase risk of TB through an association with the behaviors or conditions that directly increase the likelihood of infection or progression of TB disease [7, 8]. These indirect risk factors include alcohol consumption, illicit drug use, smoking, and socioeconomic status (SES) [6].

Figure 3. Some common direct and indirect TB risk factors



Key: Direct risk factors · Indirect risk factors · Risk factors of a weakened immune system · Outcomes of interest

Notes.
- Not all persons exposed to TB will incubate the bacteria and become infected.
- Individuals with a strong immune system are able to eliminate or suppress infectious organisms.

The following organizations, among others, provide more information on risk factors associated with TB: Centers for Disease Control and Prevention (CDC), National Institute of Allergy and Infectious Disease (NIAID), and National Library of Medicine (MedlinePlus).

The importance (that is, magnitude, prevalence) of any given risk factor relative to other risk factors may differ by population due to environmental, socio-economic, behavioral, or genetic differences.

BIOLOGICAL MECHANISMS OF TB

TB and HIV co-infection

HIV co-infection is an important risk factor due to its role as a strong immunosuppressant, reducing an infected person's defense against the TB bacteria and increasing rapid progression to TB disease or reactivation of latent TB [3, 6]. By some estimates, HIV-infected individuals are 20 times more likely to develop TB than the general population. In low-TB burden countries, the risk may be even higher: up to 37 times [3]. HIV infection exacerbates TB disease and TB infection accelerates HIV replication and progression, resulting in higher mortality rates among co-infected populations than among non-HIV infected populations [3, 6].

TB and alcohol

The role of alcohol consumption as a risk factor for TB infection or disease is primarily through its potential effects on the immune system [3, 7, 8] and is summarized in the "Alcohol consumption and immune function" section of the **Background chapter** of this Health Review.

Other indirect mechanisms include associations between alcohol consumption and other risk factors for TB exposure, infection, treatment outcomes, and mortality, as depicted in Figure 3 and described below.

- Alcohol consumption has been hypothesized to indirectly increase the risk of TB infection through an increased likelihood of being in crowded spaces or prolonged contact with an infected person [6-8].
    - However, a recent systematic review by Melsew et al. (2018) found that four out of five studies found no association between alcohol consumption and TB infectiousness, and concluded that the importance of non-clinical factors, including alcohol consumption and smoking, may be dependent on the setting, such as indoor bars [9].
- Heavy drinking may increase the risk of progression of TB disease through an increased likelihood of non-compliance with treatment or low engagement with health services or medical care [5].
- Alcohol consumption could also be a risk factor for mortality among people living with TB [3].

Summary of recent TB research

This chapter of the *IARD Health Review: Drinking and Infectious Diseases* includes studies that examine and report a risk estimate for the association between alcohol consumption and risk of being diagnosed with active TB infection (TB incidence or newly diagnosed TB) or TB mortality, as depicted in Figure 4.

The following criteria were used to select studies for inclusion in the summary of research, following a literature search using the IARD Research Database and PubMed (see Appendix 2 for search strategies and PRISMA flow diagram).

Study designs: meta-analyses (a type of study that pools data from multiple studies), pooled cohort or case-control studies, *prospective or retrospective* cohort studies, and case-control studies; systematic reviews were excluded from summary results section due to the absence of risk estimates.
Publication dates: from 2000 through June 2022
Outcomes: active tuberculosis infection (TB incidence), mortality
Exposure: at least two defined levels of alcohol consumption
Sample size: 500+ (total)

When multiple analyses were presented in a study, we included results from models that were fully adjusted and separated former drinkers from lifetime abstainers. Results of meta-analyses are presented first, followed by results of individual studies to allow comparison of risk estimates across both types of study designs.

Note: Studies that assessed alcohol consumption as AUDIT or CAGE scores without defining a corresponding level of consumption or otherwise did not describe how different alcohol categories were defined were excluded. If multiple studies assessed populations from the same cohort or survey year and used similar methods of assessing alcohol consumption, the most recent study of the group was included in this review. Furthermore, the time frame of alcohol exposure assessment varies from study to study (for example, researchers could assess a study participant's recent past or current consumption, or both), making it difficult to determine whether risk estimates reflect recent drinking patterns or the accumulation of drinking patterns over a lifetime.

In the following tables and text, we report results of studies reporting *relative risk* (RR), *odds ratio* (OR), or *hazard ratio* (HR) estimates as "risk estimates" for TB incidence and mortality. (Please see the Glossary on page 22 for sources and definitions of relative risk and *magnitude of risk* terms as weak, modest, moderate, and strong in epidemiologic research.)

In this section of the review, we report results of the four meta-analyses and the 47 individual studies that met the review inclusion criteria. In general, the available research on the role of alcohol consumption in TB may be limited by the following study characteristics:

1. More than half of the individual study designs were retrospective.
    i. 64% of individual studies were *retrospective studies*, of which 16 were cohort studies and 14 were case-control studies.
2. Many individual studies were conducted in a high TB burden country or among a sub-population at high risk for TB. Therefore, the findings from these studies may not be applicable to low TB burden countries or the general population.
    i. 36% of individual studies were conducted in high TB burden countries as defined by WHO (see Appendix Figure A1 for a list of high TB burden countries).
    ii. 26% of individual incidence studies were conducted among a sub-population at high risk for TB. High risk populations include, for example, unhoused people, HIV+ patients, or at-risk elderly population.
3. 34% of individual studies provided unadjusted risk estimates of the relationship between alcohol consumption and the risk of TB incidence or mortality. These studies did not control for confounding variables (such as age, sex, smoking, or comorbidities), therefore they did not account for the influence of confounding bias on this relationship.
4. Few studies assessed the relationship between TB risk and multiple levels of alcohol consumption measured in grams of ethanol per day or week. Instead, many studies used generalized patterns of alcohol consumption, sometimes combining nondrinkers and non-heavy drinkers. For example, some studies assessed alcohol consumption as "often versus seldom", or as "alcohol abuse versus no alcohol abuse", or "any drinking versus no drinking".
    i. 83% of studies assessed alcohol consumption as a binary variable, of which 39 were individual studies.
    ii. 21% of studies assessed alcohol consumption using a measure of alcohol volume (quantity multiplied by frequency), of which 9 were individual studies.
    iii. Seven studies assessed alcohol consumption using more than one type of measurement.

To facilitate synthesis and reporting, this review organizes meta-analysis and individual study results according to four alcohol assessment groups and across two outcomes: TB incidence and mortality among TB positive (TB+) patients. Mortality can include death before, during, or after treatment or some combination and among a general population or treatment defaulters. Table 2 identifies the classification of study-defined alcohol consumption categories by each of the four alcohol assessment groups used in this review (see Appendix Table A1, for an expansion of this table). Note that six studies and two meta-analyses assessed alcohol consumption in multiple ways.

Table 2. Alcohol consumption and TB outcome matrix

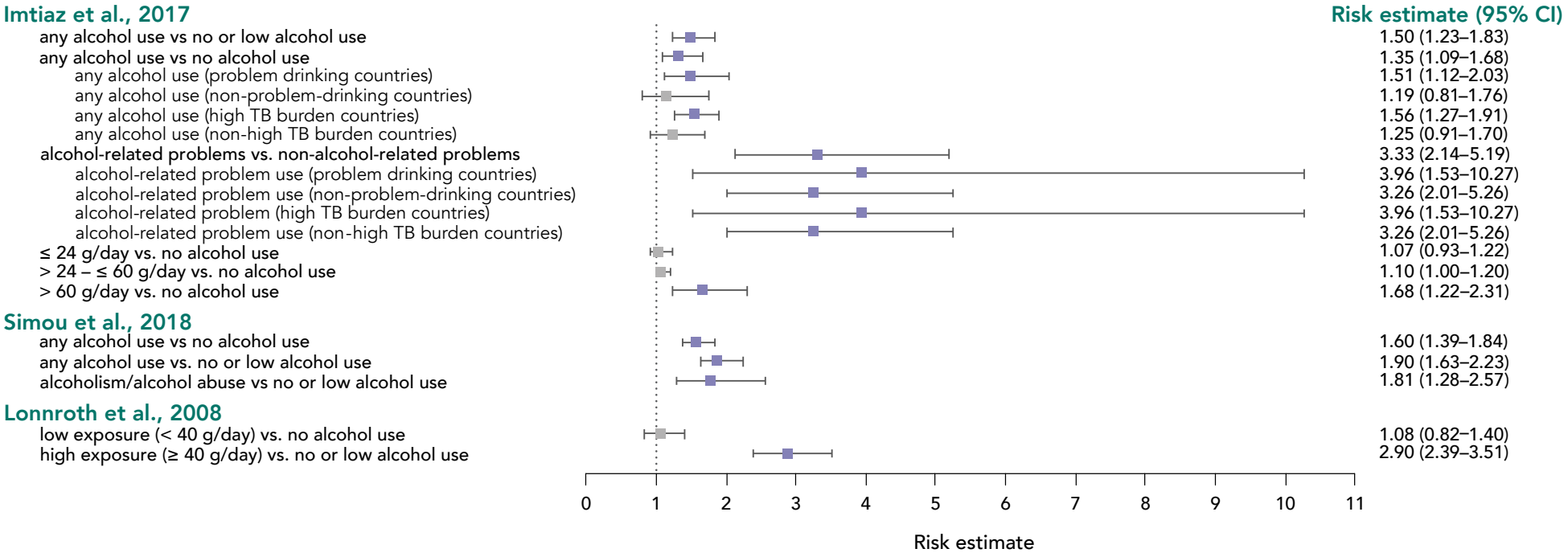
Alcohol assessment groups *Study-defined alcohol consumption categories*	TB outcomes # of studies	
	TB incidence *(Newly diagnosed TB cases)*	Mortality
Drinkers/nondrinkers *Studies that defined two alcohol consumption categories, comparing drinkers with nondrinkers, such as any alcohol use, ever drinkers vs never drinkers, highest vs. lowest consumption*	3 meta-analyses	1 meta-analysis
	10 individual	7 individual
Risky drinking/non-risky drinking *Studies that defined two alcohol consumption categories with one category indicating a heavy drinking level, such as: alcoholism, alcohol abuse, or binge drinking*	1 meta-analysis	15 individual studies
	6 individual	
Alcohol consumption frequency *Studies that defined alcohol consumption by how often alcohol is consumed, but not amount, across at least three consumption categories*	5 individual	1 individual
Alcohol consumption volume *Studies that defined alcohol consumption with a measure of both frequency of consumption and quantity of alcohol consumed*	2 meta-analyses	4 individual
	6 individual	
Total number of studies	24	28
Total without multiple exposure assessments	17	27

SUMMARY OF RECENT TB RESEARCH FROM META-ANALYSES

Three meta-analyses reported risk estimates for TB incidence (see Figure 4) [5, 7, 8] and one reported risk estimates for mortality in a TB+ population (see Figure 5) [10].

- Several analyses compared any alcohol use with no or no-to-low alcohol use and these results indicated an increased risk for TB incidence among drinkers that ranged from 35% to 90% [5, 8] and an increase in mortality that ranged from 38% to 85% [10].
    - The highest TB risk was associated with drinking in high TB burden countries as identified by WHO (see Appendix Figure A1) for TB incidence [8] and TB mortality among *multi-drug resistant TB* (MDR-TB) patients [10] or in problem drinking countries, as defined by the study authors [8].
- Among the analyses that assessed multiple drinking levels according to volume of alcohol consumption, results indicated an increased risk of TB incidence at each study's heaviest drinking level category, > 40 g/day [7] and > 60 g/day [8], and no association with TB risk at lower drinking levels.
- For mortality among TB patients, the meta-analysis by Ragan and colleagues (2020) found that TB patients in the highest alcohol consumption categories had higher mortality risk than those in the lowest drinking category, which included nondrinkers in most of the underlying studies [10].

Figure 4. Forest plot of the association between alcohol consumption and risk of TB incidence reported by meta-analyses



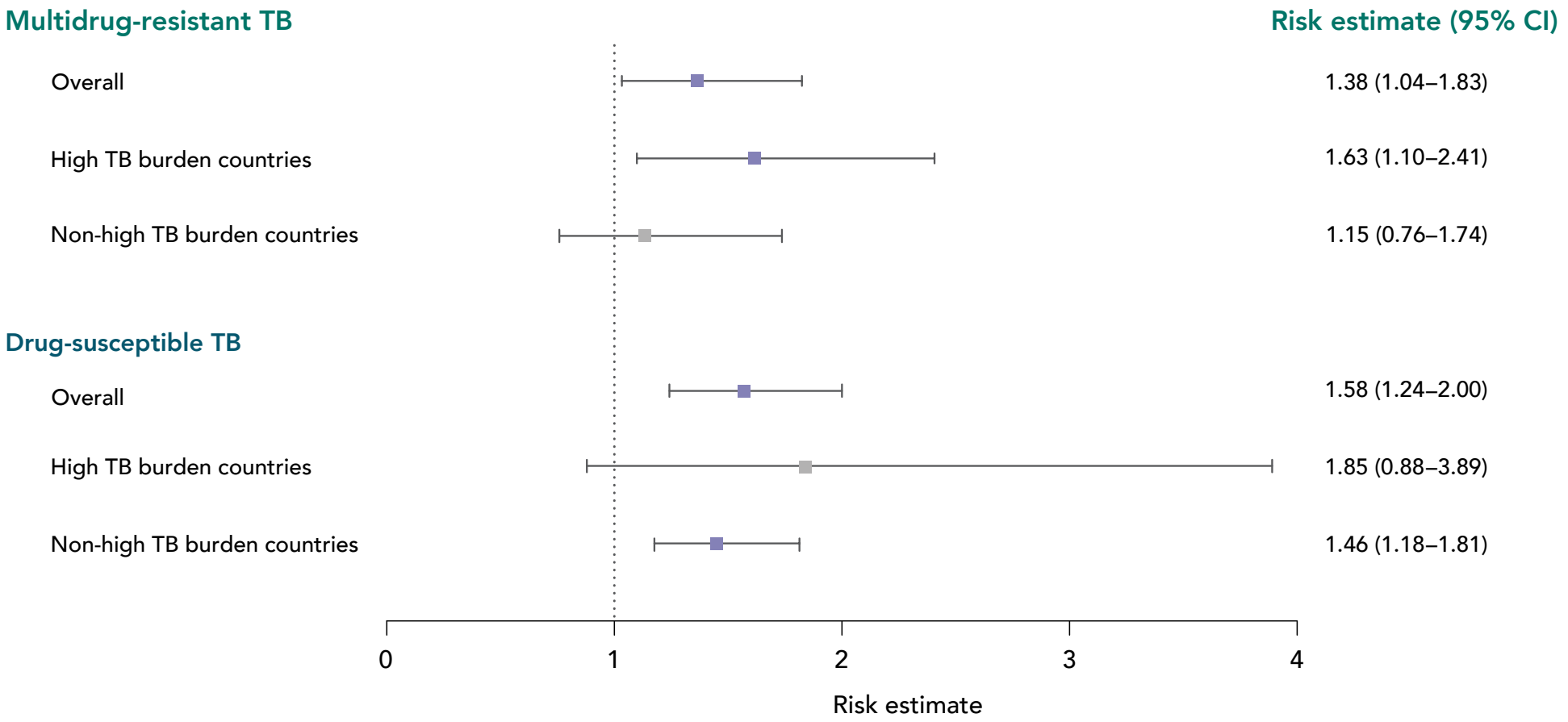
Key:

- Increased risk association
- No risk association

Figure Notes:

- See Appendix 1: Figure A2 for assistance on how to read and interpret results of a forest plot.

Figure 5. Forest plot of the association between alcohol consumption (highest compared to lowest) and mortality risk among TB+ patients, reported in Ragan et al., 2020, grouped by TB drug resistance



Key:
Increase risk association
No risk association

Figure Notes:

▶ See Appendix 1: Figure A2 for assistance on how to read and interpret results of a forest plot.

SUMMARY OF RECENT TB RESEARCH FROM INDIVIDUAL STUDIES

Active TB incidence

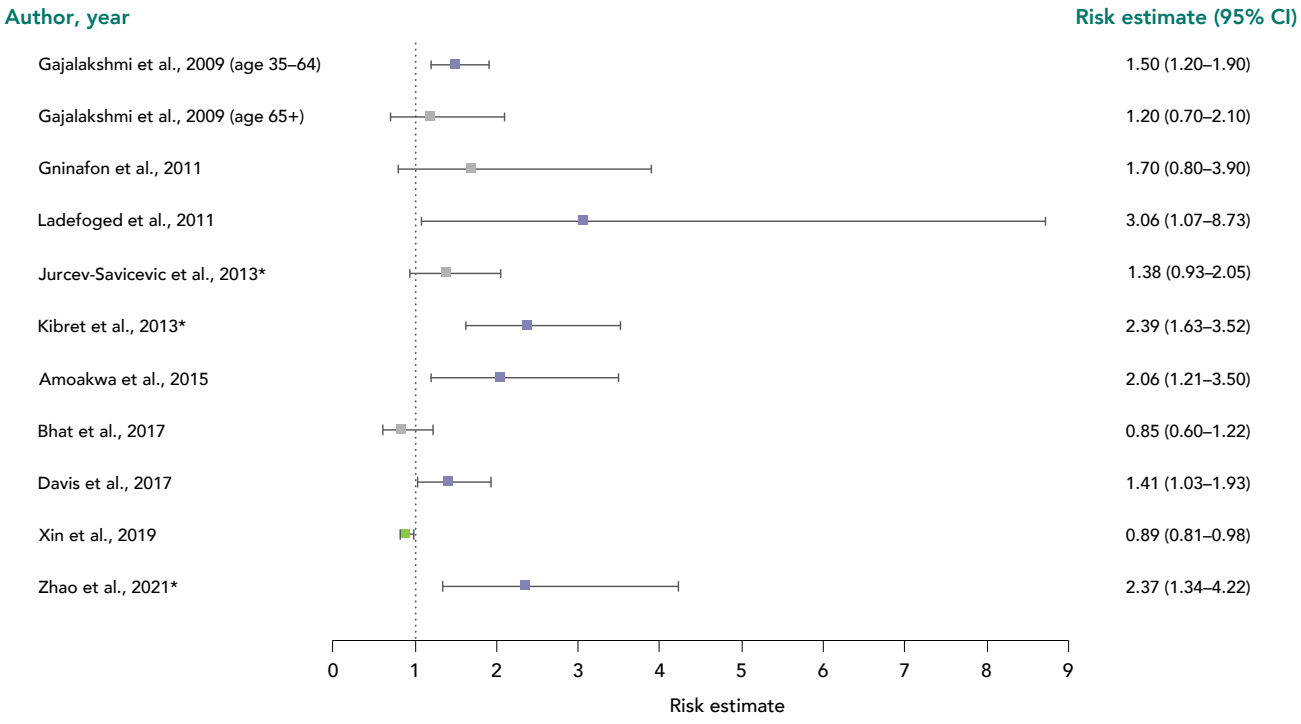
Twenty-one individual studies met the review criteria and examined the association between alcohol consumption and TB incidence (see Appendix 1: Table A2 for study descriptions) [11-31].

Nondrinkers vs drinkers

Ten individual studies contributing 11 risk estimates and examined the association between alcohol consumption, assessed as drinkers compared to nondrinkers, and TB incidence (see details in Appendix 1: Table A2) [11, 12, 14-16, 20-22, 28, 31].

- Among the 11 risk estimates, six indicated an increased TB risk associated with any alcohol consumption [11, 14, 15, 21, 22, 31], four found no association [12, 15, 16, 20], and one reported a reduced risk [28] (see Figure 6).
  - The magnitude of increased risk for drinkers compared to nondrinkers ranges from 1.4 to 3.1 for risk estimates that reached statistical significance. See Glossary for descriptions of these risk estimates as "modest" to "strong", and "weak" for the reduced risk estimate reported by Xin et al. 2019 [32].

Figure 6. Forest plot of the association between drinkers and the risk of TB incidence compared to nondrinkers



Key:
- Increased risk association
- No risk association
- Decreased risk association

Figure Notes:

- See Appendix 1: Figure A2 for assistance on how to read and interpret results of a forest plot.

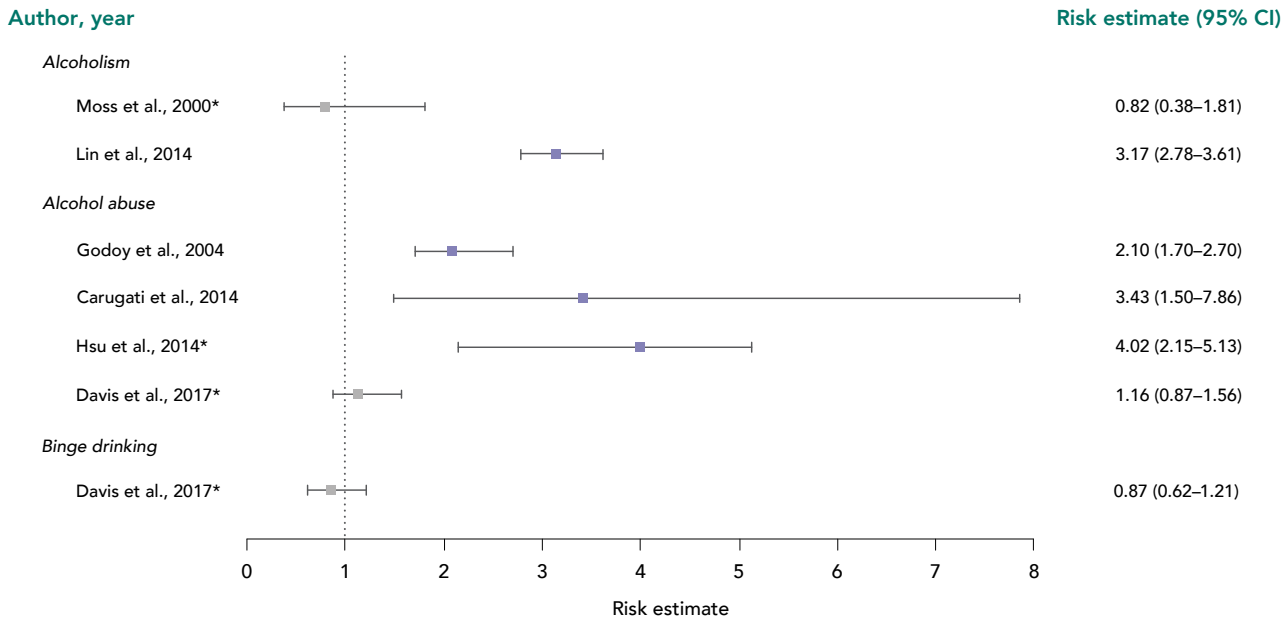
** This study provided unadjusted risk estimates only.*

Non-risky drinking vs risky drinking

Six individual studies contributing seven risk estimates examined the association between alcohol consumption, assessed as risky drinking compared to non-risky drinking, and TB incidence (see Appendix 1: Table A2) [13, 14, 17, 18, 24, 25].

- Non-risky drinking included drinkers and nondrinkers in all studies.
- Among seven risk estimates, four indicated an increased risk of TB infection associated with risky drinking compared with non-risky drinking [13, 17, 18, 24] and three found no association [14, 25] (see Figure 7).
  - The magnitude of increased risk for consumers engaging in risky drinking ranged from 2.10 to 4.02 for risk estimates that reached statistical significance. See Glossary for descriptions of these risk estimates as "moderate" to "strong" [32].

Figure 7. Forest plot of the association between risky drinking and the risk of TB incidence compared to non-risky drinking, by study-defined alcohol consumption



Key:
Increased risk association
No risk association

Figure Notes:

- See Appendix 1: Figure A2 for assistance on how to read and interpret results of a forest plot.

** This study provided unadjusted risk estimates only.*

Alcohol consumption frequency

Five individual studies examined the association between alcohol consumption, assessed as frequency of consumption, and TB incidence (see Appendix 1: Table A2) [14, 20, 23, 26, 29].

- One of three studies comparing drinkers to nondrinkers reported an increased risk of TB incidence associated with consuming alcohol more than once a week (see Table 3) [29].
- Two of three studies comparing risk across current drinkers only found that risk increased among those who consumed alcohol daily, compared to those who drank alcohol less often (see Table 3) [20, 23].

Table 3. Risk of TB incidence associated with frequency of alcohol consumption

Study	Nondrinkers	Former drinkers	Less than monthly	Monthly	2-3 times monthly	Once a week	2-3 times weekly	4-6 times weekly	Daily
Phyo et al., 2019†	ref.					1.20 (0.90–1.50)			1.00 (0.70–1.40)
Davis et al., 2017	ref.	3.43 (2.45–4.80)	1.12 (0.82–1.54)		1.17 (0.74–1.85)		1.92 (0.55–6.66)	1.27 (0.30–5.35)	
Yen et al., 2018†	ref.			0.87 (0.57–1.33)		1.77 (1.32–2.37)			
Jurcev-Savicevic et al., 2013*			ref.			2.42 (0.97–6.07)			3.86 (1.56–9.55)
Li et al., 2021	1.16 (1.00–1.35)			ref.					1.45 (1.14–1.84)

† Reference group may include nondrinkers, former drinkers, or occasional drinkers or a combination.
Note. This table includes all individual prospective cohort, retrospective cohort, and case-control study designs that were published between 2000 and August 2022 and reported risk estimates for different drinking frequencies.

Table Notes:

- Vertical bars correspond to the lower and upper limits of each drinking frequency category as defined by the study authors.
- Purple shading indicates a statistically significant increase in relative risk compared to the reference category.
- Green shading indicates a statistically significant decrease in relative risk compared to the reference category.
- Grey shading indicates that the study did not assess risk at this drinking level.
- White shading indicates that the relative risk for that drinking category was not statistically different from the risk for the reference category.

Alcohol consumption volume

Six individual studies examined the association between alcohol consumption, assessed in volume of consumption (grams per day), and TB incidence (see Table 4 for risk estimates and see Appendix 1: Table A2 for study descriptions) [11, 19, 25, 27, 28, 30].

- Of the five studies reporting on men and women combined, three indicated an increased risk of TB infection associated with each study's heaviest drinking category compared to nondrinkers starting at 14g [11], 20g [27], 30g [30], or more per day.
  - One study found no difference in TB risk among current drinkers consuming up to 20 g/day and > 20 g/day [25]; nondrinkers were not included.
  - Two studies reported a reduced risk associated with each study's lowest alcohol consumption category, compared to nondrinkers [27, 28].
  - However, Amoakwa et al., (2015) and Soh et al., (2017) define consumption at any level greater than 14 g and 20 g per day, respectively, as their heaviest consumption categories[11, 27]. These wide consumption level categories limit the ability to differentiate results for moderate, or heavy drinking levels, compared to nondrinkers.
- One study grouped results by sex and reported an increased risk of TB for men starting at 50 g/day or more but found no association for women [19].
- The magnitude of increased risk ranged from 1.24 to 2.87 for risk estimates that reached statistical significance. See Glossary for descriptions of these risk estimates as "moderate" to "strong" [32].

Table 4. Risk of TB incidence associated with volume of alcohol consumption

Study Reference	Sex	Nondrinker	0–10	10–20	20–30	30–40	40–50	50–60	60–70	70–80	80–90	90–100+
Moss et al., 2000	Combined		ref.		0.76 (0.32–1.81)							
Xin et al., 2019	Combined	ref.†	0.82 (0.81–0.98)	0.87 (0.74–1.02)	0.94 (0.82–1.08)			0.97 (0.83–1.12)				
Amoakwa et al., 2015	Combined	ref.†	1.74 (0.89–3.41)	2.30 (0.95–5.55)	2.87 (1.30–6.32)							
Soh et al., 2017	Combined	ref.†	0.83 (0.71–0.97)	1.06 (0.73–1.53)	1.45 (1.11–1.90)							
Yoo et al., 2021	Combined	ref.†	0.94 (0.89–1.00)		1.24 (1.13–1.36)							
Jee et al., 2009	Men	ref.†	1.00 (0.90–1.10)		1.10 (1.00–1.20)		1.30 (1.20–1.40)					1.60 (1.40–1.90)
Jee et al., 2009	Women	ref.†	1.00 (1.00–1.10)				0.60 (0.20–2.50)					

† Reference group may include nondrinkers, former drinkers, or occasional drinkers or a combination.
Note. This table includes all individual prospective cohort study designs that were published between 2000 and August 2022 and reported risk estimates for drinking at multiple levels.

Table Notes:

- Vertical bars correspond to the lower and upper limits of each drinking level as defined by the study (converted, if necessary, to grams of pure alcohol per day).
- Purple shading indicates a statistically significant increase in relative risk compared to the reference group.
- Green shading indicates a statistically significant decrease in relative risk compared to the reference group.
- Grey shading indicates that the study did not assess risk at this drinking level.
- White shading indicates that the risk for that drinking level was not statistically significant from the risk for the reference group.

Summary of TB incidence

Seventy-one percent of the studies included in this section of the review assessed alcohol consumption as a binary variable (nondrinkers versus drinkers and non-risky drinking versus risky drinking), with just over half finding an increased risk of TB incidence associated with the drinker group. A stronger association was observed for risky drinking (compared to non-risky drinking) than for any drinking (compared to nondrinkers), suggesting that TB risk may increase with higher levels of consumption. This observation is supported by the results of the five studies that assessed alcohol consumption using average volume in grams per day. All of these studies reported an increased risk in the heavier alcohol consumption categories as defined by each study, but not in the lower categories. However, the wide range in average alcohol volume included in these categories makes it difficult to determine whether risk truly increases at 14 g/day, 20 g/day, 30 g/day, or some other level.

Risk of mortality among TB+ patients

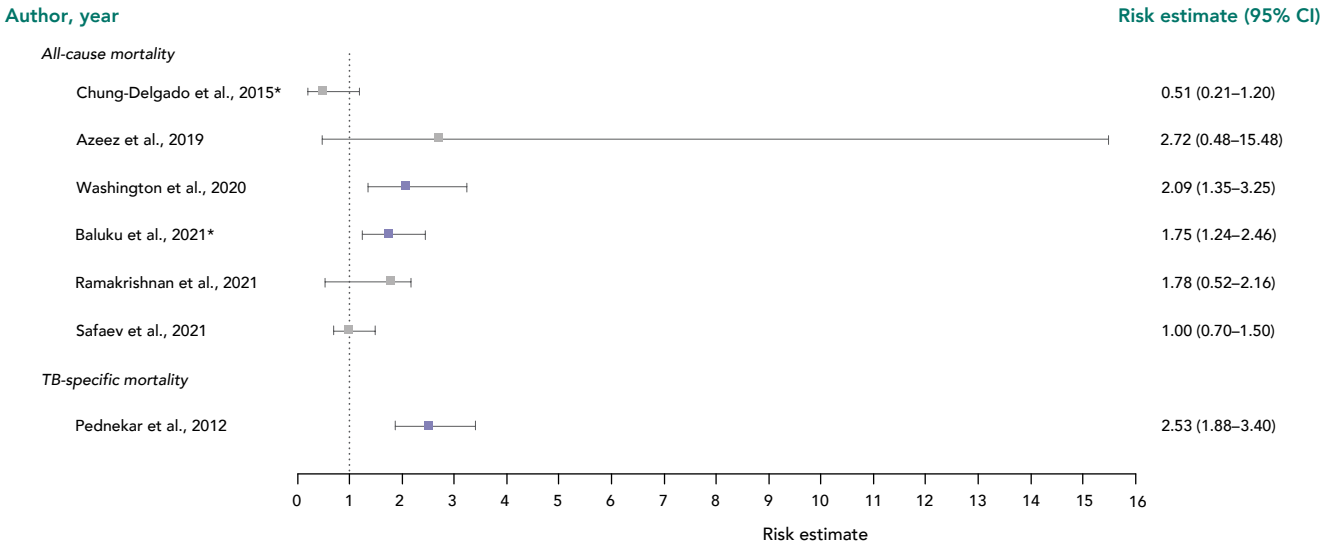
Twenty-seven individual studies met the review criteria for examining the association between alcohol consumption and mortality among TB+ patients (see Appendix 1: Table A3 for study descriptions) [19, 33-58].

Nondrinkers vs drinkers

Seven individual studies examined the association between alcohol consumption, assessed as drinkers compared to nondrinkers, and mortality among TB+ patients (see Figure 8 for risk estimates and Appendix 1: Table A3 for study descriptions) [33-39].

- Three studies reported an increased risk in mortality among TB+ patients associated with alcohol consumption compared to nondrinkers [34, 36, 39], one of which reported on TB-specific mortality [36].
    - The magnitude of increased risk ranged from 1.75 to 2.53 for risk estimates that reached statistical significance. See Glossary for descriptions of these risk estimates as “modest” to “moderate” [32].
- Four studies found no association between alcohol consumption and mortality [33, 35, 37, 38].

Figure 8. Forest plot of the association between drinkers and the risk of mortality among TB+ patients compared to nondrinkers



Key:
Increased risk association
No risk association

** This study provided unadjusted risk estimates only.*

Figure Notes:

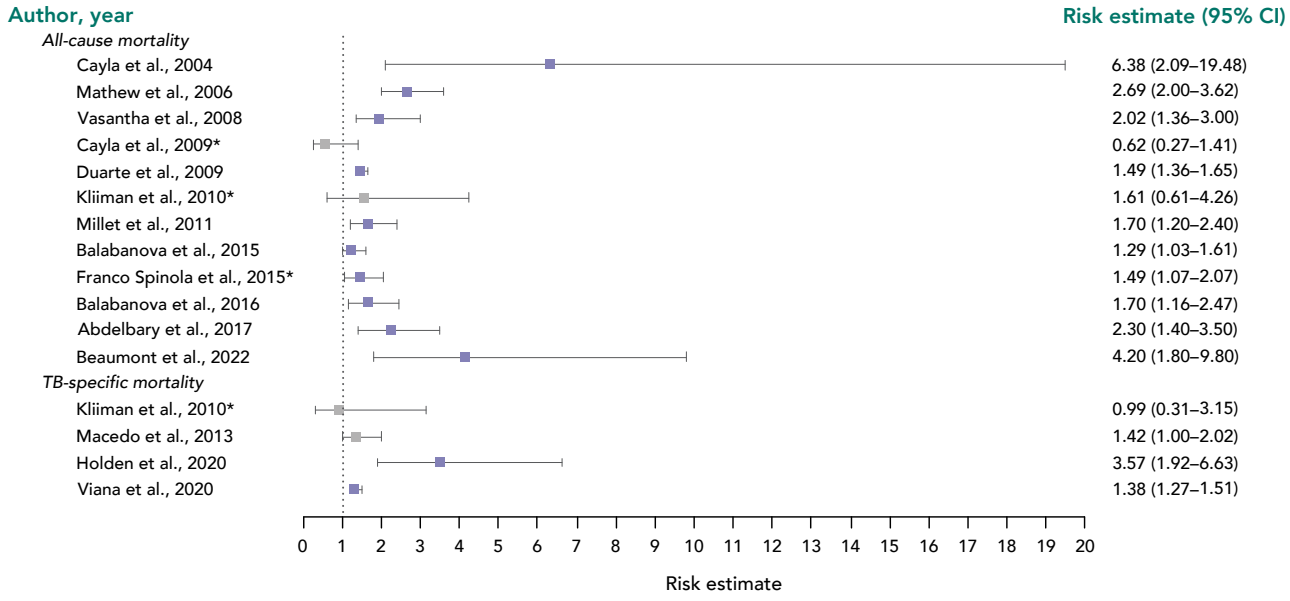
- See Appendix 1: Figure A2 for assistance on how to read and interpret results of a forest plot.

Non-risky drinking vs risky drinking

Fifteen individual studies contributing 16 risk estimates examined the association between alcohol consumption, assessed as risky drinking compared to non-risky drinking, and mortality among TB+ patients (see Figure 9 for risk estimates and Appendix 1: Table A3 for study descriptions) [40-54].

- For mortality from any cause, 10 out of 12 studies found an increased risk associated with risky drinking among people with TB disease [40-42, 44, 46, 48-54].
- For mortality attributed to TB, two out of four studies found an increased risk associated with risky drinking compared to non-risky drinking [52, 53].
  - The magnitude of increased mortality risk ranged from 1.29 to 6.38 for risk estimates that reached statistical significance. See Glossary for descriptions of these risk estimates as "weak" to "strong" [32].

Figure 9. Forest plot of the association between risky drinking and the risk of mortality among TB+ patients compared to non-risky drinking



Key:
Increased risk association
No risk association

** This study provided unadjusted risk estimates only.*

Figure Notes:

- See Appendix 1: Figure A2 for assistance on how to read and interpret results of a forest plot.

Alcohol consumption frequency

One study examined the association between alcohol consumption, assessed as frequency of consumption, and mortality among TB+ patients [55] (see Appendix 1: Table A3 for study description). This study found no association among men and women combined [55].

Alcohol consumption volume

Four individual studies examined the association between alcohol consumption, assessed in volume of consumption (grams per day), and mortality among TB+ patients [19, 56-58] (see Appendix 1: Table A3 for study description).

- Three studies reported on all-cause mortality. Two of the studies found an increased risk associated with alcohol consumption starting at 14g [58] and 16g [56] per day, and one study reported no association between any level of consumption and mortality risk [57], compared to nondrinkers (see Table 5).
  - However, Sterling et al., (2006) and Baez-Saldana et al., (2016) only examine current consumption greater than 14 g and 16 g per day, respectively [56, 58]. This limits the ability to differentiate results for moderate or heavy drinking levels, compared to light drinking levels.
- The magnitude of increased mortality risk ranged from 1.31 to 2.94 for risk estimates that reached statistical significance for the heaviest alcohol consumption category (as defined by the authors). See Glossary for descriptions of these risk estimates as "weak" to "moderate" [32].

Table 5. Risk of mortality associated with volume of alcohol consumption among TB+ patients

Study Reference	Sex	Nondrinker	Former Drinkers	0–10	10–20	20–30	30–40	40–50	50–60	60–70	70–80	80–90	90–100	100–150	150–200+
Mortality															
Bonnet et al., 2016*	Combined	ref.†		0.82 (0.50–1.36)										0.89 (0.18–4.31)	
Sterling et al., 2006	Combined			ref.										2.94 (1.71–5.05)	
Baez-Saldana et al., 2016	Combined			ref.										1.90 (1.33–2.73)	
TB-specific mortality															
Baez-Saldana et al., 2016	Combined			ref.										1.56 (0.51–4.82)	
Jee et al., 2009	Men	ref.†		0.91 (0.77–1.08)										1.31 (0.86–1.97)	
Jee et al., 2009	Women	ref.†		0.78 (0.48–1.26)											

* This study provided unadjusted risk estimates only.
† Nondrinker (may include former or occasional drinkers or both).
Note. This table includes all individual prospective and retrospective cohort study designs that were published between 2000 and August 2022 and reported risk estimates for drinking at multiple levels.

Table Notes:

- Vertical bars correspond to the lower and upper limits of each drinking category as defined by the study (converted, if necessary, to grams of pure alcohol per day).
- Purple shading indicates a statistically significant increase in relative risk compared to the reference category.
- Green shading indicates a statistically significant decrease in relative risk compared to the reference category.
- Grey shading indicates that the study did not assess risk at this drinking category.
- White shading indicates that the relative risk for that drinking category was not statistically different from the risk for the reference category.

Summary of mortality among TB+ patients

Eighty-one percent of the studies included in this section of the review assessed alcohol consumption as a binary variable. When compared to nondrinkers, most studies reported no association between drinkers and risk of mortality; however, when compared to non-risky drinking, 80% of studies reported an increased risk of mortality associated with risky drinking. This stronger association with mortality risk among risky drinkers than among drinkers overall may indicate that mortality risk may increase with increasing levels of consumption. When alcohol consumption was assessed as average volume in grams per day, most analyses did not find an association between alcohol consumption and mortality risk. Two studies, both comparing light drinking to heavier drinking, reported an increased risk of mortality for their heaviest drinking category, starting at 14 g/day and 16 g/day. However, the wide range in average alcohol volume included in these categories makes it difficult to determine whether risk truly increases at 14 g/day, or at 40 g/day, or at some other level.

Future Research

Many risk factors for TB are interrelated, making it difficult for researchers to sufficiently assess their independent effects, as suggested in a 2013 systematic review by Fox and Menzies. For example, poverty is correlated with crowded housing, smoking, lack of access to health care, and lack of access to food and high-quality food. Aging contributes to a progressive decline in immune function that is associated with an increase in chronic diseases—both aging and co-occurring chronic disease increase the risk of TB [3].

Overall, the findings in this review were inconclusive due to the limitations of the available research: assessment of alcohol consumption as a binary variable, time frame of alcohol exposure assessment, utilization of retrospective study designs and preponderance of high-risk study populations. Future studies applying more rigorous methods to quantify alcohol consumption (for example, in grams per day or grams per week) are needed to provide insight into whether the association between drinking and TB changes according to light, moderate, and heavy levels of consumption [10]. More studies considering lifetime alcohol exposure are needed to better understand risk in relation to drinking patterns over a lifetime. Furthermore, more prospective studies are needed using nationally representative populations to prevent recall bias [5, 8] and to provide a better understanding of the role alcohol plays as a risk factor for TB in a general population.

Glossary

- **Hazard ratio (HR)** measures how often an event or outcome (for example, tuberculosis) occurs in one group (for example, drinkers) compared to how often it happens in another group (for example, nondrinkers) and is commonly used to measure survival. A hazard ratio equivalent to one (HR = 1) means no difference in outcome occurrence between both groups and a hazard ratio greater than or less than one (HR > 1 or HR < 1) means outcome occurred in one group more than the other.

- **Immune response** consists of two systems: the adaptive immune response and the innate immune response.

  - The **innate immune response** is the immediate responder part of the immune system and is non-specific to an invading pathogen. Whereas the **adaptive immune response** is activated in the presence of a specific pathogen or antigen; it can recognize and immediately defend against a previously encountered antigen, but it can also be activated by the innate immune response [59].

- **Multi-drug resistant TB** is a disease caused by bacteria resistant to two specific anti-TB drugs: isoniazid and rifampin.

  - **Drug-susceptible TB** is a disease that will respond to multiple anti-TB drugs during treatment.

- **Odds ratio (OR)** is a measure of association between an exposure (for example, alcohol) and an outcome (for example, tuberculosis) and is more commonly used in case-control studies. An odds ratio above one (OR > 1) indicates higher odds of the outcome, an odds ratio equal to one (OR = 1) indicates no effect on the odds, and an odds ratio less than one (OR < 1) indicates lower odds of the outcome.

- **Prospective studies** select a study population and assess the exposure of interest (for example, current or past alcohol consumption, or both) and track the study population over time to determine whether the outcome of interest (for example, tuberculosis) occurred within the follow-up period.

- **Relative risk** is a measure that compares the probability of a given outcome (for example, TB) among a group of people with a given risk factor (for example, alcohol consumption) with the probability of that outcome among a group of people without the risk factor (for example, nondrinkers). A risk estimate above one (RR > 1) indicates an increased risk of the outcome associated with the exposure and a risk estimate below one (RR < 1) indicates a reduced risk of the outcome associated with the exposure. If the risk estimate is equivalent to one (RR = 1) then there is no association between the outcome and the exposure.

  - The **magnitude of relative risk** describes the strength of the association between the exposure and outcome of interest, or the relative risk estimate. There are several terms used to describe or interpret different relative risk estimates.

Some commonly used descriptors are weak, small, moderate, medium, strong, or large [32, 60-63], however, the risk estimates associated with each term may differ or overlap (see Figures 10A–C). For example, according to Schoenbach and Rosamond 2000 [32], a moderate risk is equivalent to a relative risk of 1.8 to 3.0, while Craun and Calderon n.d., states that moderate to strong risk is equivalent to a relative risk greater than 1.5 [60, 62].

Figure 10A. Descriptions of magnitude of risk

1.0	No association (null value)
1.1–1.3	Weak
1.4–1.7	Modest
1.8–3.0	Moderate
3–8	Strong

Source: Schoenbach and Rosamond 2000 [32]

Figure 10B. Descriptions of magnitude of risk

	Trivial	Small	Moderate	Large	Very Large	Nearly perfect	Perfect
Correlation	0.0	0.1	0.3	0.5	0.7	0.9	1
Diff. in means	0.0	0.2	0.6	1.2	2.0	4.0	infinite
Freq. diff.	0	10	30	50	70	90	100
Rel. risk	1.0	1.2	1.9	3.0	5.7	19	infinite
Odds ratio	1.0	1.5	3.5	9.0	32	360	infinite

Source: Hopkins 2002 [60]

Figure 10C. Descriptions of magnitude of risk

Effect size: Interpretation suggestions for social science data

Type of effect size estimate	Included indices	RMPE	Moderate effect	Strong effect
Group difference	d, Δ, g	0.41	1.15	2.70
Strength of association	r, R, φ, p, partial r, β, rh, tau	0.2	0.5	0.8
Squared association indices	r^2, R^2, η^2, adjusted R^2, ω^2 ε^2	0.04	0.25	0.64
Risk estimates	RR, OR	2.0*	3.0	4.0

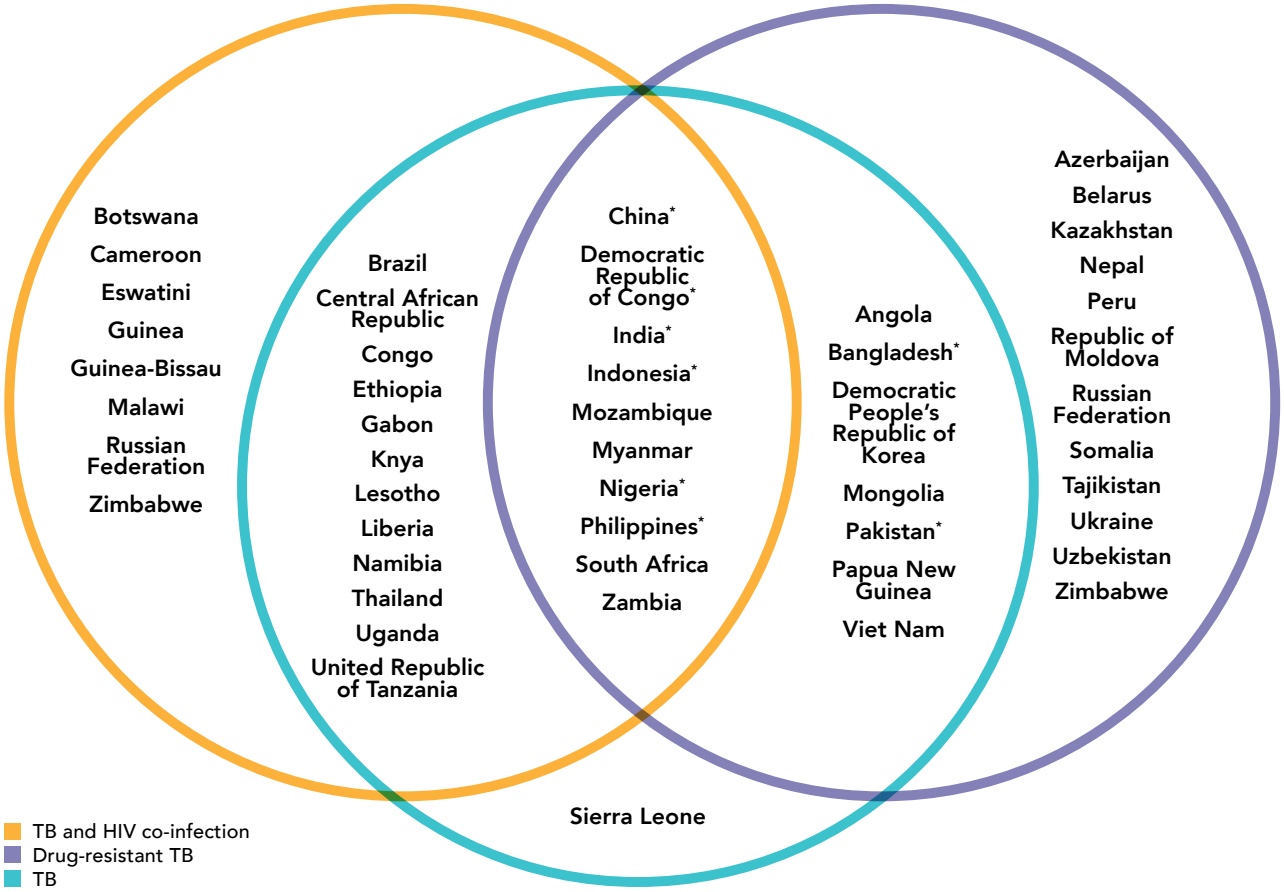
**These are not anchored to r and should be interpreted with caution.*
Note. RMPE = recommended minimum effect size representing a "practically" significant effect for social science data. For effects with highly valid dependent measures (e.g., death) and using rigorous controlled outcomes trials, lower values may have practical value. RR = relative risk; OR = odds ratio.

Source: Ferguson 2016 [61]

- **Retrospective studies**, such as case-control or retrospective cohort studies, begin with identification of individuals with the outcome of interest (for example, tuberculosis) and then assess participants' recent or past exposure (for example, alcohol consumption).

Appendix 1

Figure A1: High-burden countries for TB, TB and HIV co-infection, and drug-resistant TB from the World Health Organization, Global Tuberculosis Report 2022.



**One of the eight countries that accounted for the majority of the new TB diagnoses in 2021.*

Figure A2. Understanding and interpreting forest plots.

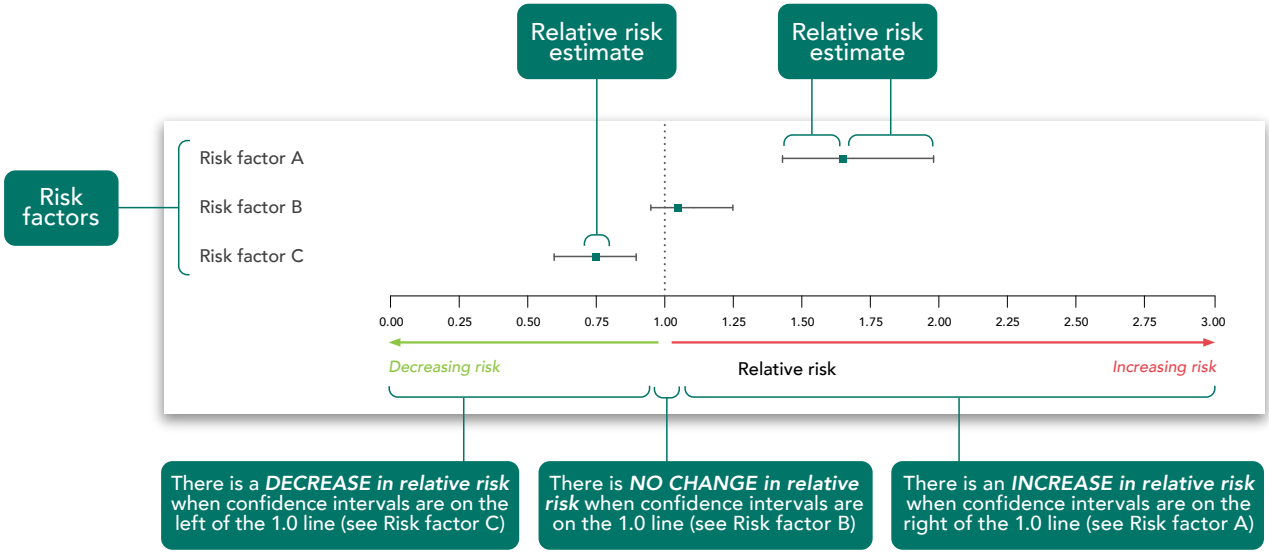


Table A1. Description of studies that assessed the relationship between the compared alcohol consumption categories and risk of TB incidence and mortality

Alcohol assessment groups		TB outcomes	
		TB incidence (newly-diagnosed TB infection)	Mortality
Total meta-analyses		3	1
Total individual studies		21	27
Drinkers/nondrinkers *Studies that defined two alcohol consumption categories that compare drinkers with nondrinkers, such as any alcohol use, ever drinkers versus never drinkers, highest versus lowest consumption*			
Baluku 2021	Alcohol use (yes/none)		✓
Ramakrishna, 2021	Alcohol use in past 12 months (yes/no)		✓
Safaev, 2021	Alcohol use (yes/no or not reported)		✓
Zhao, 2021	Drinking alcohol (yes/no)	✓	
Ragan, 2020 (meta-analysis)	High vs. no or low alcohol consumption		✓
Washington, 2020	History of regular (daily) consumption (yes/no)		✓
Azeez, 2019	Alcohol use (yes/no)		✓
Xin, 2019*	Current drinking (consumption in the past 12 months) (yes/no)	✓	
Simou, 2018 (meta-analysis)*	Alcohol use (any/no and any/no or low)	✓	
Bhat, 2017	Alcohol consumption (yes/no)	✓	
Davis, 2017*	Ever drank alcohol (yes/no)	✓	
Imtiaz, 2017 (meta-analysis)*	Alcohol use (any/no and any/no or low	✓	
Amoakwa, 2015*	Alcohol use (use/no use)	✓	
Chung-Delgado, 2015	Alcohol use (yes/no)		✓
Jurcev-Savicevic, 2013*	Alcohol consumption (non-consumer/ex-consumer and non-consumer/current consumer)	✓	
Kibret, 2013	Alcohol drinking (yes/no)	✓	
Pednekar, 2012	Alcohol use (never users vs. ever users or past and present users)		✓
Gninafon, 2011	Daily use of alcoholic beverages (yes/no)	✓	
Ladefoged, 2011	Often or ≥ 1/week vs. seldom or < 1/week	✓	
Gajalakshmi, 2009	Alcohol use or ≥ 1/month vs. nonuser or < 1/month	✓	
Risky drinking/non-risky drinking *Studies that defined two alcohol consumption categories with one category indicating a heavy drinking level, such as alcoholism, alcohol abuse, or binge drinking*			
Beaumont, 2022	Alcohol abuse or > 10 units/week (yes/no)		✓
Holden, 2020	Alcohol abuse or > 14 units/week for women and > 21 units/week for men (yes/no)		✓
Viana, 2020	Alcoholism (yes/no)		✓

Continued on next page

Table A1. Description of studies that assessed the relationship between the compared alcohol consumption categories and risk of TB incidence and mortality *(Continued)*

Simou, 2018 (meta-analysis)*	Alcoholism or alcohol abuse vs. no or low alcohol	✓	
Abdelbary, 2017	Alcoholism (yes/no)		✓
Davis, 2017*	Alcohol abuse determined by CAGE scores (yes/no)	✓	
	Binge drank in the past 90 days (yes/no)	✓	
Imtiaz, 2017 (meta-analysis)*	Alcohol-related problems (yes/no)	✓	
Balabanova, 2016	Alcohol abuse (yes/no)		✓
Balabanova, 2015	Alcohol abuse determined by self-reporting and physician assessment (yes/no)		✓
Franco Spinola, 2015	Excess alcohol use (yes/no)		✓
Carugati, 2014	Alcohol abuse defined as 3+ drinks/day or 5+ drinks at one time 1+/week (yes/no)	✓	
Macedo, 2013	Alcoholism (yes/no)		✓
Godoy, 2004	Alcohol abuse (yes/no)	✓	
Hsu, 2014	Alcohol abuse defined by ICD 10 codes (yes/no)	✓	
Lin, 2014	Alcoholism (yes/no)	✓	
Millet, 2011	Alcohol abuse defined as > 168 g/week for women and > 280 g/week for men (yes/no)		✓
Kliiman, 2010	Alcohol abuse defined as ≥ 7 drinks/week for women and ≥ 14 drinks/week for men (yes/no)		✓
Cayla, 2009	Alcohol use defined as > 168 g/week for women and > 280 g/week for men (yes/no)		✓
Duarte, 2009	Alcoholism (reported/not reported or unknown)		✓
Vasantha, 2008	Alcoholism (yes/no)		✓
Mathew, 2006	Alcoholism (yes/no)		✓
Cayla, 2004	Alcoholics defined as > 168 g/week for women and > 280 g/week for men (yes/no)		✓
Moss, 2000*	Alcoholism as determined by CAGE score (yes/no)	✓	
Alcohol consumption frequency *Studies that defined alcohol consumption by how often alcohol is consumed, but not amount, across at least three consumption categories*			
Li, 2021	Alcohol consumption: non-drinker, monthly to weekly (ref.), daily	✓	
Phyo, 2019	Alcohol consumption: weekly, daily, never (ref.)	✓	
Yen, 2018	Alcohol use: none (ref.), < 1/week, 1+/week	✓	
Davis, 2017*	Frequency of alcohol consumption: never drank alcohol (ref.), monthly or less; 2–4 times/month, 2–3 times/week, 4+ times/week, does not currently drink	✓	
Theron, 2015	Alcohol consumption: never (ref.), social, regular, heavy		✓
Jurcev-Savicevic, 2013*	Frequency of alcohol consumption in the last 12 months: < 1/week (ref.), 1+/week, daily	✓	

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Table A1. Description of studies that assessed the relationship between the compared alcohol consumption categories and risk of TB incidence and mortality *(Continued)*

Alcohol consumption volume *Studies that defined alcohol consumption with a measure of both frequency of consumption and quantity of alcohol consumed*			
Yoo, 2021	Alcohol consumption: moderate or < 30 g/day, heavy or 30+ g/day, none or 0 g (ref.)	✓	
Xin, 2019*	Alcohol consumption: non-drinkers (ref.), < 10 g/day, 10–20 g/day, 20–50 g/day, ≥ 50 g/day,	✓	
Lonnroth, 2018 (meta-analysis)	Level of exposure: low exposure or < 40 g/day vs. no alcohol use, high exposure or ≥ 40 g/day vs. no or low alcohol use	✓	
Imtiaz, 2017 (meta-analysis)*	Ethanol intake in grams per day: no alcohol use (ref.), ≤ 24, > 24 – ≤ 60, > 60	✓	
Soh, 2017	Alcohol intake: non-drinkers (ref.), monthly to weekly, 1 drink daily, 2+ drinks daily,	✓	
Baez-Saldana, 2016	> 10 drinks/week (yes/no)		✓
Bonnet, 2016	Alcohol consumption, daily: none (ref.), < 5 drinks/week, ≥ 5 drinks/week		✓
Amoakwa, 2015*	Alcohol units per week: none (ref.), 0–4 units/ week, 5–10 units/week, > 10 units/week	✓	
Jee, 2009	Alcohol drinking, g/day: Incidence: nondrinker (ref.), < 25, 25–49.9, 50–99.9, > 100.0 Mortality: nondrinker (ref.), < 50, ≥ 50	✓	✓
Sterling, 2006	Daily alcohol use in past 5 years defined as ≥ 1 drink/day (yes/no)		✓
Moss, 2000*	Alcoholism: < 10 drinks/week (ref.), ≥ 10 drinks/week	✓	

* Indicates a study with multiple methods of alcohol consumption.

Table A2. Description of studies that compared different levels of alcohol consumption and the risk of TB incidence

Author, year	Study design*	Location	Includes high TB burden countries (Y/N)?	Study population or Study inclusions†	Includes high risk population (Y/N)?	Sex	Age group (years)	Reference group	Alcohol exposure	Risk estimate (95% CI)‡
Nondrinkers versus drinkers										
Amoakwa et al., 2015	P-C	South Africa (Soweto)	Y	HIV+ black individuals in prevention trial regimens with no active TB diagnosis and no initiation of ART treatment; 83% were female	Y	combined	18+	alcohol no use	alcohol use	2.06 (1.21–3.50)
Bhat et al., 2017	C-C	India (Gwalior district, Madhya Pradesh)	Y	Survey-based, Saharia tribe (one of three particularly vunerable tribal groups), cases were TB+ (79% male) and controls were TB- (49% male) from the same village	Y	combined	15+	no alcohol consumption	alcohol consumption	0.85 (0.60–1.22)
Davis et al., 2017	C-C	Kazakhstan (Almaty City and the Almaty, Kyzylorda, and Kostanay oblasts)	N	Surveillance-based data, cases were TB+ patients from high and low TB burden sites and one community and one household control for each case.	Y	combined	18+	never drank alcohol	drank alcohol	1.41 (1.03–1.93)
Gajalakshmi et al., 2009	C-C	India (Thiruvallur district, Tamil Nadu)	Y	Clinical-based data, cases were TB+ patients receiving treatment for the first time and controls were TB- from rural communities	Y	male	35–64	non-alcohol users	alcohol users	1.50 (1.20–1.90)
							65+	non-alcohol users	alcohol users	1.20 (0.70–2.10)
Gninafon et al., 2011	C-C	Benin (Cotonou)	N	Health facility-based, cases were TB+ patients with no long term treatment exposure, two controls were selected from neighborhoods of each case; majority were male	N	combined	15+	no daily use of alcoholic bevarages	daily use of alcoholic beverages	1.70 (0.80–3.90)
Jurcev -Savicevic et al., 2013	C-C	Croatia (seven randomly-selected countries; 53.9% of Croatia)	N	Seven randomly selected counties from 2006–2008; Cases were TB+ adults and controls with no history of TB were found from general practitioners' records and were matched	N	combined	15+	non-consumer	current consumer	1.38 (0.93–2.05)‡
									ex-consumer	1.71 (0.97–3.03)‡
Kibret et al., 2013	C-C	Ethiopia (Addis Ababa)	Y	Two hospital- and 13 health center-based data, cases were HIV+/TB+ after ART initiation and controls were HIV+/TB- after ART initiation	Y	combined	18+	no alcohol drinking	alcohol drinking	2.39 (1.63–3.52)‡

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Table A2. Description of studies that compared different levels of alcohol consumption and the risk of TB incidence *(Continued)*

Imtiaz et al., 2017	MA	Worldwide	Y	1. cohort or case-control studies 2. reporting RRs for alcohol consumption as a risk factor for tuberbulosis (relative risks, hazard ratios, or odds ratios) 3. tuberculosis incidence, new or recurrent	Y	combined	all ages	no alcohol use	alcohol use	1.35 (1.09–1.68)
		High TB burden countries	Y		Y					1.56 (1.27–1.91)
		Non-high TB burden countries	N		N					1.25 (0.91–1.70)
		Problem drinking countries	N		Y					1.51 (1.12–2.03)
		Non-problem drinking countries	N		Y					1.19 (0.81–1.76)
		Worldwide	Y		Y	male				1.12 (0.73–1.71)
		High TB burden countries	Y		Y					1.46 (1.20–1.79)
		Non-high TB burden countries	N		N					1.05 (0.40–2.81)
		Problem drinking countries	N		Y					1.30 (1.07–1.57)
		Non-problem drinking countries	N		Y					1.03 (0.11–9.54)
		Worldwide	Y		Y	female				1.20 (0.54–2.67)
		High TB burden countries	Y		Y					
		Non-high TB burden countries	N		N					1.20 (0.54–2.67)
		Problem drinking countries	N		Y					1.80 (0.51–6.41)
		Non-problem drinking countries	N		Y					0.54 (0.27–1.07)
Simou et al., 2018	MA	Worldwide	Y	1. cohort/logitudinal, case-control, cross-sectional studies 2. Alcohol consumption as exposure group with reference group as no alcohol consumption or lowest exposed category 3. outcome is active TB	Y	combined	18+	no drinking	drinking	1.60 (1.39–1.84)

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Table A2. Description of studies that compared different levels of alcohol consumption and the risk of TB incidence *(Continued)*

Ladefoged et al., 2011	C-C	Greenland	N	Cases were TB+ patients identified at 13 district hospitals, healthy controls were age and sex-matched to cases from the same hospital district	N	combined	4+	seldom (never or ≤ 2 days/ week)	often (> 2 days/week)	3.06 (1.07–8.73)#
Xin et al., 2019	P-C	China (Zhongmu County)	Y	At-risk elderly population from rural communities , cases are TB+ and controls TB-	Y	combined	50–70	no alcohol drinking	alcohol drinking	0.89 (0.81–0.98)
Zhao et al., 2021	C-C	China	Y	Hospital-based patients, cases had diagnosed active TB and were age- and sex-matched with physical examinees as controls	Y	combined	30+	no alcohol drinking	alcohol drinking	2.37 (1.34–4.22)‡
Non-risky drinking versus risky drinking										
Carugati et al., 2014	C-C	Italy (Milan)	N	Hospital-based HIV+ patients with presumptive active TB in metropolitan area. The TB group was made up of culture positive TB patients, the non-TB group consisted of culture negative patients	Y	combined	18+	No alcohol abuse	alcohol abuse	3.43 (1.50–7.86)‡
Davis et al., 2017	C-C	Kazakhstan (Almaty City and the Almaty, Kyzylorda, and Kostanay oblasts)	N	Surveillance-based data, cases were TB+ patients from high and low TB burden sites and one community and one household control for each case	Y	combined	18+	No alcohol abuse	alcohol abuse	1.16 (0.87–1.56)‡
								No binge drinking in the past 90 days	binge drinking in the past 90 days	0.87 (0.62–1.21)‡
Godoy et al., 2004	C-C	Spain (Catalonia)	N	Surveillance data and health center data from 13 autonomous communities; Cases were new TB+ patients and controls were those with negative test results	N	combined	> 1	No alcohol abuse	alcohol abuse	2.10 (1.70–2.70)
Hsu et al., 2014	C-C	Taiwan	N	National Health Insurance Research 1996–2008 Dataset, cases were patients with active TB or reactivation of TB and matched with 10 controls based on age, sex, and month, year of visit from Registry of Beneficiaries of the NHIRD	N	combined	n/a	No alcohol abuse	alcohol abuse	4.02 (2.15–5.13)‡
Lin et al., 2014	C-C	Taiwan	N	Cirrhortic cohorts and non-cirrhotic cohorts from National Health Insurance Research 1998–2007 Dataset	Y	combined	20+	No alcoholism	alcoholism	3.17 (2.78–3.61)

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Table A2. Description of studies that compared different levels of alcohol consumption and the risk of TB incidence *(Continued)*

Imtiaz et al., 2017	MA	Worldwide	Y	1. cohort or case-control studies 2. reporting RRs for alcohol consumption as a risk factor for tuberbulosis (relative risks, hazard ratios, or odds ratios) 3. tuberculosis incidence, new or recurrent	Y	combined	all ages	non-alcohol related problems	alcohol related problems	3.33 (2.14–5.19)
		High TB burden countries	Y		Y	combined			alcohol related problems	3.96 (1.53–10.27)
		Non-high TB burden countries	N		N	combined			alcohol related problems	3.26 (2.01–5.26)
Simou et al., 2018	MA	Worldwide	Y	1. cohort/logitudinal, case-control, cross-sectional studies 2. Alcohol consumption as exposure group with reference group as no alcohol consumption or lowest exposed category 3. outcome is active TB	Y	combined	18+	no alcohol abuse/ alcoholism	alcohol abuse/ alcoholism	1.81 (1.28–2.57)
Moss et al., 2000	P-C	United States (San Francisco, California)	N	Unhoused population recruited through shelters and food lines; majority males	Y	combined	n/a	No alcoholism	alcoholism	0.82 (0.38–1.81)‡
Alcohol frequency consumption										
Davis et al., 2017	C-C	Kazakhstan (Almaty City and the Almaty, Kyzylorda, and Kostanay oblasts)	N	Surveillance-based data, cases were TB+ patients from high and low TB burden sites and one community and one household control for each case	Y	combined	18+	never drank alcohol	monthly or less	1.12 (0.82–1.54)‡
									2–4 times a month	1.17 (0.74–1.85)‡
									2–3 times a week	1.92 (0.55–6.66)‡
									4 or more times a week	1.27 (0.30–5.35)‡
									does not currently drink	3.43 (2.45–4.80)‡
Jurcev-Savicevic et al., 2013	C-C	Croatia (seven random counties; 53.9% of Croatia)	N	Seven randomly selected counties from 2006–2008; Cases were TB+ adults and controls with no history of TB were found from general practicioners' records and were matched	N	combined	15+	less than once a week in the past year	at least once a week in the past year	2.42 (0.97–6.07)‡
									daily drinker in the past year	3.86 (1.56–9.55)‡
Li et al., 2021	P-C	Singapore	N	Chinese adult citizens or permanent residents of Singapore who participated in the Sinapore Chinese Health Study between 1993 and 1998	N	combined	45–74	monthly-weekly drinker	daily drinker	1.45 (1.14–1.84)
									nondrinker	1.16 (1.00–1.35)

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Table A2. Description of studies that compared different levels of alcohol consumption and the risk of TB incidence *(Continued)*

Phyo et al., 2019	P-C	Mandalay, Myanmar	Y	HIV+ adults enrolled in Integrated HIV Care receiving ART at a general hospital and prison hospital	Y	combined	15+	never consumed alcohol	daily alcohol consumption	1.00 (0.70–1.40)
									weekly alcohol consumption	1.20 (0.90–1.50)
Yen et al., 2018	P-C	Taiwan	N	Participants in 2001, 2005, and 2009 surveys from the National Health Interview Survey (NHIS) with no history of TB diagnoses	N	combined	18+	No alcohol use	alcohol use less than once a week	0.87 (0.57–1.33)
									alcohol use more than once a week	1.77 (1.32–2.37)
Alcohol volume consumption										
Amoakwa et al., 2015	P-C	South Africa (Soweto)	Y	HIV+ black individuals in prevention trial regimens with no active TB diagnosis and no initiation of ART treatment; 83% were female	Y	combined	18+	None	0–4 units/week	1.74 (0.89–3.41)
									5–10 units/ week	2.30 (0.95–5.55)
									> 10 units/ week	2.87 (1.30–6.32)
Imtiaz et al., 2017	MA	Worldwide	Y	1. cohort or case-control studies 2. reporting RRs for alcohol consumption as a risk factor for tuberbulosis (relative risks, hazard ratios, or odds ratios) 3. tuberculosis incidence, new or recurrent	Y	combined	all ages	no alcohol use	≤ 24 g/day	1.07 (0.93–1.22)
									> 24– ≤ 60 g/ day	1.10 (1.00–1.20)
									> 60 g/day	1.68 (1.22–2.31)
Jee et al., 2009	P-C	South Korea	N	South Koreans participating in the National Health Insurance Corporation medical evaluation between 1992 and 1995	N	males	30+	nondrinker	< 25 g/day	1.00 (0.90–1.10)
									25–50 g/day	1.10 (1.00–1.20)
									50–100 /day	1.30 (1.20–1.40)
									≥ 100 g/day	1.60 (1.40–1.90)
						female		nondrinker	<25 g/day	1.00 (1.00–1.10)
									25–50 g/day	
									50–100 g/day	0.60 (0.20–2.50)
									≥ 100g/day	

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Table A2. Description of studies that compared different levels of alcohol consumption and the risk of TB incidence *(Continued)*

Lonnoroth et al., 2008	MA	Worldwide	Y	1. cohort or case-control studies 2. reporting ORs for alcohol consumption as a risk factor for tuberbulosis 3. active TB disease	Y	combined	n/a	nondrinker	< 40 g/day	1.08 (0.82–1.40)‡
									> 40 g/day	4.08 (2.49–6.68)
Moss et al., 2000	P-C	United States (San Francisco, California)	N	Unhoused population recruited through shelters and food lines; majority males	Y	combined	n/a	< 10 drinks/ week	≥ 10 drinks/ week	0.76 (0.32–1.81)‡
Soh et al., 2017	P-C	Singapore	N	Chinese adult citizens or permanent residents of Singapore who participated in the Singapore Chinese Health Study between 1993 and 1998 with no history of TB	N	combined	45–74	nondrinker	Monthly to weekly drinker	0.83 (0.71–0.97)
									1 drink/day	1.06 (0.73–1.53)
									2+ drinks/day	1.45 (1.11–1.90)
Xin et al., 2019	P-C	China (Zhongmu County)	Y	At-risk elderly population from rural communities , cases are TB+ and controls TB-	Y	combined	50–70	nondrinker	< 10 g/day	0.82 (0.71–0.94)
									10–20 g/day	0.87 (0.74–1.02)
									20–50 g/day	0.94 (0.82–1.08
									> 50 g/day	0.97 (0.83–1.12)
Yoo et al., 2021	P-C	South Korea	N	South Koreans aged 66+ who participated in the National Screening Program for Transitional Ages between 2009 and 2014, no diagnosis of TB or any registered disabilities	Y	combined	66+	nondrinker	mild	0.94 (0.89–1.00)
									heavy	1.24 (1.13–1.36)

* MA = meta-analysis, C-C = case-control, P-C = prospective cohort
† For meta-analyses study inclusions criterias were described instead of study population.
‡ Risk estimates are unadjusted estimates
# Study combined non-drinkers with occasional drinkers or low-to-moderate drinkers

Table A3. Description of studies that compared different levels of alcohol consumption and the risk of mortality among a TB+ population

Author, year	Study design*	Location	Includes high TB burden countries (Y/N)?	Study population or Study inclusions†	Sex	Age group (years)	Reference group	Alcohol exposure	Risk estimate (95% CI)‡
Nondrinkers versus drinkers									
Azeez et al., 2019	R-C	South Africa (East London, Eastern Cape)	Y	TB+/HIV+ patients on ART treatment who started TB treatment	combined	mean 38	no alcohol use	alcohol use	2.73 (0.48–15.48)
Ragan et al., 2020	MA	Worldwide	Y	Drug susceptible TB+ patients receiving treatment from 80 studies	combined	16+	non-alcohol group	alcohol group	1.85 (0.88–3.89)‡
		High TB burden countries	Y						2.86 (1.94–4.21)‡
		Non-high TB burden countries	N						1.58 (1.24–2.00)‡
		Worldwide	Y	MDR-TB+ patients receiving treatment from 31 studies					1.38 (1.04–1.83)‡
		High TB burden countries	Y						1.63 (1.10–2.41)‡
		Non-high TB burden countries	N						1.15 (0.76–1.74)‡
Baluku et al., 2021	R-C	Uganda	Y	DR-TB+ patients with a poor progonistic indicator in treatment from 16 DR-TB hospitals	combined	28–45	no alcohol use	alcohol use	1.75 (1.24–2.46)‡
Chung-Delgado et al., 2015	R-C	Peru (Lima)	N	MDR-TB+ patients from hospitals and control health centers who completed treatment	combined	18+	no alcohol use	alcohol use	0.51 (0.21–1.20)‡
Pednekar et al., 2012	P-C	India (Mumbai)	Y	Residents in the main city of Mumbai	male	45+	never users	ever users	2.53 (1.88–3.40)#
Ramakrishnan et al., 2021	P-C	India (Puducherry, Cuddalore, and Villupuram)	Y	New TB+ drug sensitive patients who started treatment under NTP (National Tuberculosis Program) in three districts in India; majority of patients were males (79%)	combined	15+	no alcohol use	alcohol use	1.78 (0.52–2.16)
Safaev et al., 2021	R-C	Uzbekistan (Tashkent)	N	TB+ patients who are MDR/RR+ and XDR+ and enrolled in treatment in Uzbekistan	combined	all ages	no alcohol use	alcohol use	1.00 (0.70–1.50)
Washington et al., 2020	P-C	India (Karnataka and Telangana)	Y	TB+ patients who started treatment and were residents of 61 cities/towns in Karnataka and eight cities/towns in Telangana	combined	18+	does not drink alcohol	drinks alcohol	2.09 (1.35–3.25)

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Table A3. Description of studies that compared different levels of alcohol consumption and the risk of mortality among a TB+ population *(Continued)*

Non-risky drinking versus risky drinking									
Abdelbary et al., 2017	P-C	Mexico (Tamaulipas)	N	Newly diagnosed TB+ patients reported at the Tamaulipas health department	combined	18+	no alcoholism	alcoholism	2.30 (1.40–3.50)
Balabanova et al., 2015	P-C	Russia (Samara Oblast)	N	New and re-treated TB+/HIV- patients from 14 civilian hospitals and clinics; majority of patients were male (75.7%)	combined	mean 39	no alcohol abuse	alcohol abuse	1.29 (1.03–1.61)
Balabanova et al., 2016	P-C	Eastern Europe (Lithuania, Latvia, Estonia, Romania)	N	New and re-treated MDR-TB and XDR-TB patients from four hospitals with mostly male patients (79%)	combined	15+	no alcohol abuse	alcohol abuse	1.70 (1.16–2.47)
Beaumont et al., 2022	R-C	France (Paris)	N	Pan-susceptible TB+ patients from two hospitals, mostly male patients (69%)	combined	18+	no alcohol abuse	alcohol abuse	4.2 (1.8–9.8)
Cayla et al., 2004	P-C	Spain	N	TB+ patients from SEPAR who started treatment between 1999 and 2000 at 76 different hospitals	combined	all ages	not alcoholic	alcoholic	6.38 (2.09–19.48)
Cayla et al., 2009	P-C	Spain	N	TB+ patients from SEPAR diagnosed between 2006 and 2007 who started treatment from 53 hospitals	combined	18+	no alcohol use	alcohol use (men over 280 g/week and women over 160 g/week)	0.62 (0.27–1.41)‡
Duarte et al., 2009	C-C	Brazil	Y	Cases are patients who died from any cause during initial TB treatment and controls are patients who were cured after completing TB treatment; data obtained from SINAN for patients with TB from 2000 to 2004. Most cases were male (72.55%), as were most controls (62.30%)	combined	all ages	no alcoholism	alcoholism	1.49 (1.36–1.65)
Franco Spinola et al., 2015	C-C	Portugal (Northern region)	N	Cases were TB+ patients underoing treatment and controls who completed treatment between 2008 and 2012; cases were mostly male (81%), as were controls (67%)	combined	all ages	no excessive alcohol use	excessive alcohol use	1.49 (1.07–2.07)‡
Holden et al., 2020	R-C	Denmark	N	TB+ patients from Danish National Patient Registry from 2009 and 2014	combined	> 0	no alcohol abuse	alcohol abuse	3.57 (1.92–6.63)#
Kliiman et al., 2010	R-C	Estonia	N	TB+ patients who started treatment between 2003 and 2005. Information was collected from the Estonian TB Registry	combined	all ages	no alcohol abuse	alcohol abuse	1.61 (0.61–4.26)‡ 0.99 (0.31–3.15)‡#
Ribeiro Macedo et al., 2013	P-C	Brazil	Y	TB+ prisoners identified through SINAN (a national information system) between 2007 and 2011 who completed treatment	combined	18+	no alcoholism	alcoholism	1.42 (1.00–2.02)‡#
Mathew et al., 2006	R-C	Russia(Western Siberia Tomsk Oblast)	N	TB+ patients who died during therapy in Tomsk Oblast	combined	18+	no alcoholism	alcoholism	2.69 (2.00–3.62)

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Table A3. Description of studies that compared different levels of alcohol consumption and the risk of mortality among a TB+ population *(Continued)*

Millet et al., 2011	R-C	Spain (Barcelona)	N	TB+ patients who completed treatment and drug susceptibility testing between October 1995 and 1997 that were detected by the Barcelona TB control program. Most patient were male (68.2%).	combined	median 36	no alcohol abuse	alcohol abuse	1.70 (1.20–2.40)
Vasantha et al., 2008	R-C	India (Tiruvallur district)	Y	TB+ patients from government health facilities in 209 villages receving treatment, mostly comprising of males (73%)	combined	all ages	no alcoholism	alcoholism	2.02 (1.36–3.00)
Viana et al., 2020	R-C	Brazil	Y	New TB+ patients from SINAN who started treatment between 2008 and 2013 with information from two national data sources	combined	> 0	no alcoholism	alcoholism	1.38 (1.27–1.51)‡#
Alcohol frequency consumption									
Theron et al., 2015	P-C	South Africa (Cape Town, Durban), Zimbabwe (Harare), Zambia (Lusaka) and Tanzania (Mbeya)	Y	TB symptomatic patients from primary care clinics who later had confirmed TB and were provided treatment	combined	18+	never	social	0.81 (0.50–1.27)‡
								regular	0.83 (0.50–1.36)‡
								heavy	0.62 (0.15–1.77)‡
Alcohol volume consumption									
Sterling et al., 2006	P-C	North America (US and Canada)	N	TB+ patients enrolled in 29 clinics and receiving TB therapy	combined	18+	no daily alcohol use (< 1 drink/day)	daily alcohol use (≥ 1 drink/day)	2.94 (1.71–5.05)
Jee et al., 2009	P-C	South Korea	N	South Koreans participating in the National Health Insurance Corporation medical evaluation between 1992 and 1995	male	n/a	nondrinker	< 50 g/day	0.91 (0.77–1.08)#
								≥ 50 g/day	1.31 (0.86–1.97)#
					female		nondrinker	< 50 g/day	0.78 (0.48–1.26)#
								≥ 50g/day	
Baez-Saldana et al., 2016	P-C	Mexico (Veracruz State)	N	TB+ patients who are drug susceptible	combined	15+	< 10 drinks/week	> 10 drinks/week	1.90 (1.33–2.73)
									1.56 (0.51–4.82)#
Bonnet et al., 2016	R-C	Georgia (Abkhazia), Armenia, Uzbekistan (Karakalpakstan), Kenya (Nairobi), Swaziland (Shiselweni)	N	TB+ patients with confirmed MDR either before starting MDR-TB treatment or a month or less after treatment initiation	combined	18+	none	moderate	0.82 (0.50–1.36)‡
								excessive	0.89 (0.18–4.31)‡

* MA = meta-analysis, C-C = case-control, P-C = prospective cohort, R-C = retrospective cohort
† For meta-analyses study inclusions criterias were described instead of study population.
‡ Risk estimates are unadjusted estimates
# Risk estimate is for TB-specific mortality

Appendix 2

SEARCH STRATEGIES

Systematic reviews/Meta analyses

IARD Research Database

1. IARD databases=Research; Document date on or after '01 Jan 2010' and (IARD keywords equals 'meta analysis, review' or Composite phrase 'systematic review' or Composite phrase 'narrative review' or Composite phrase 'scoping review' or Composite phrase 'critical review' or Composite phrase 'literature review') and (Composite all words 'tuberculosis' or (IARD keywords equals 'respiratory disease, respiratory system' and IARD keywords equals 'infections')) in Research
    - Search Date: 28 Feb 2022

2. IARD databases=Research; Text=("tuberculosis" OR (("respiratory disease" OR "respiratory system") AND "infections")) AND ("meta analysis" OR "systematic review"); Publish From=2000-01-01; Publish To=2009-12-31
    - Search date 14 Aug 2022

3. IARD databases=Research; Text="tuberculosis" AND ("meta analysis" OR "systematic review"); Publish From=2000-01-01; Date Added From=2022-08-31
    - Search date: 31 Aug 2022

Pubmed Database

1. Pubmed Search: "Tuberculosis"[Mesh] AND ("Alcohol Drinking"[Mesh] OR "Alcohol-Related Disorders"[Mesh] OR alcohol*[TIAB] OR drink*[TIAB]) Limited to Meta Analyses, Reviews or Systematic Reviews from 2010
    - Search Date: 20 April 2022

2. Revised Pubmed Search: ("Tuberculosis"[Mesh] OR tuberculosis[TIAB]) AND ("Alcohol Drinking"[Mesh] OR "Alcohol-Related Disorders"[Mesh] OR alcohol*[TIAB] OR drink*[TIAB]) AND ("Review"[Publication Type] OR "Systematic Review"[Publication Type] OR "Meta-Analysis"[Publication Type] OR "systematic review"[TIAB] OR "meta analysis"[TIAB])
    - Search Date: 04 June 2022

3. Pubmed Search: "Tuberculosis"[Mesh] AND ("Alcohol Drinking"[Mesh] OR "Alcohol-Related Disorders"[Mesh] OR alcohol*[TIAB] OR drink*[TIAB]) limited to Meta Analysis OR Systematic Review AND Publication date 2000-2010 - English language only
    - Search Date: 14 August 2022

4. Pubmed Search: ("Tuberculosis"[Mesh] OR "Tuberculosis"[TI]) AND ("Alcohol Drinking"[Mesh] OR "Alcohol-Related Disorders"[Mesh] OR alcohol*[TIAB] OR drink*[TIAB]) AND 2022/03:2022/09[EDAT] AND (("meta analysis"[PT] OR "systematic review"[PT]) OR ("meta analysis"[TIAB] OR "systematic review"[TIAB]))
    - Search Date: 31 August 2022

Individual Studies

IARD Research Database

1. IARD search: Document date on or after '01 Jan 2010' and Publication type equals 'Research Paper' and (Composite all words 'tuberculosis' or (CBA keywords equals 'respiratory disease, respiratory system' and CBA keywords equals 'infections'))
    - Search Date: 25 May 2022

2. IARD databases=Research; Text="tuberculosis"; Keywords="prospective study" OR "retrospective study" OR "case control study" OR "observational study"; Publication Types=Research Paper; Publish From=2000-01-01; Publish To=2010-01-01
    - Search Date: 14 Aug 2022

3. IARD databases=Research; Text="tuberculosis"; Keywords="prospective study" OR "retrospective study" OR "case control study" OR "observational study"; Publish From=2000-01-01; Date Added From=2022-05-24
    - Search Date: 31 Aug 2022

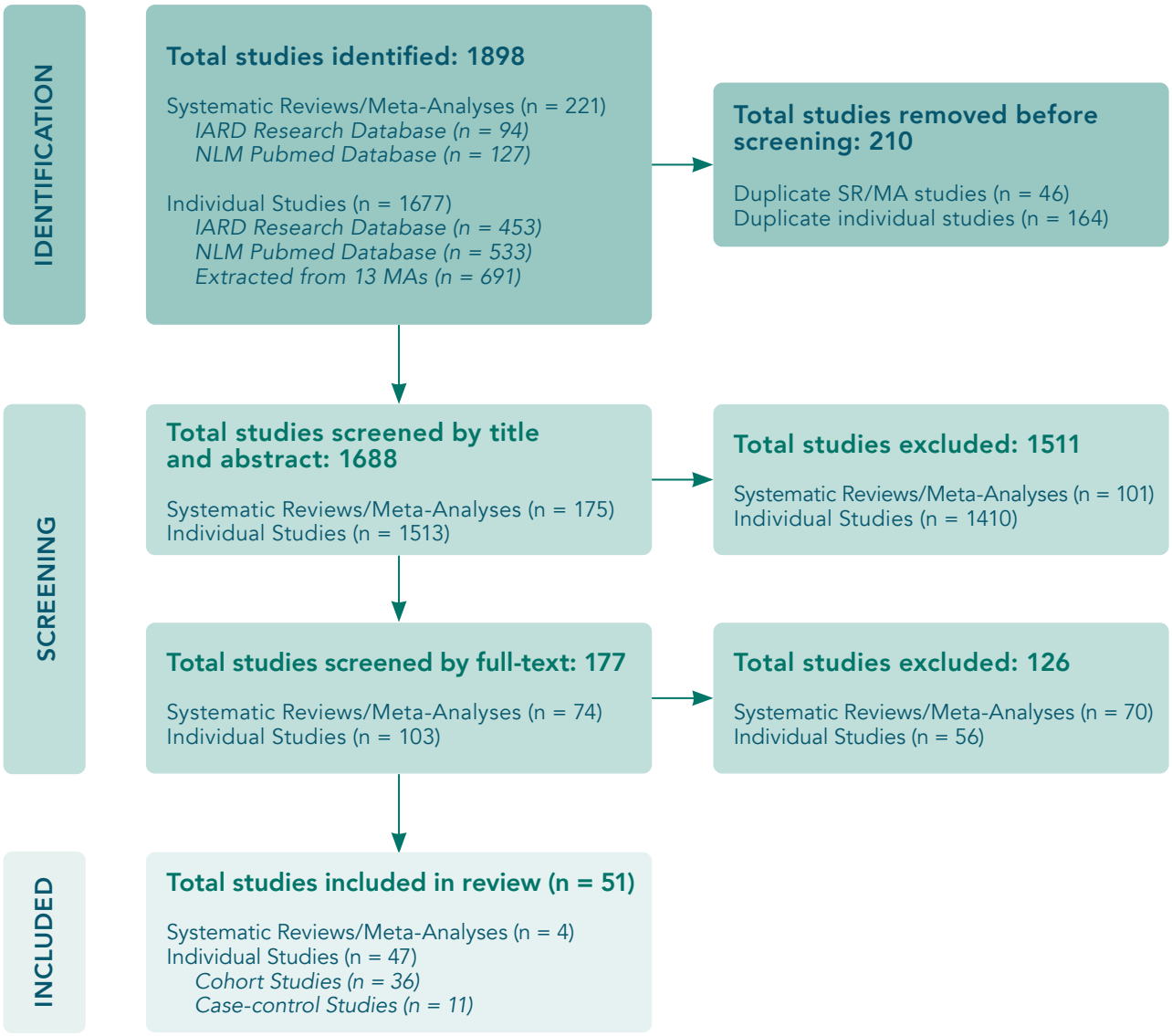
Pubmed Database

1. Pubmed search: ("Tuberculosis"[Mesh] OR tuberculosis[TIAB]) AND ("Alcohol Drinking"[Mesh] OR "Alcohol-Related Disorders"[Mesh] OR alcohol*[TIAB] OR drink*[TIAB]) AND ("Cohort Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Retrospective Studies"[Mesh] OR cohort[TIAB] OR longitudinal*[TIAB] OR "prospective study"[TIAB] OR "retrospective study"[TIAB] OR "control study"[TIAB] OR "Controlled Clinical Trial" [Publication Type]) Limited to articles from 2010
    - Search Date: 30 May 2022

2. Pubmed search: "Tuberculosis"[Mesh] AND ("Alcohol Drinking"[Mesh] OR "Alcohol-Related Disorders"[Mesh] OR alcohol*[TIAB] OR drink*[TIAB]) AND ("Cohort Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Retrospective Studies"[Mesh] OR cohort[TIAB] OR longitudinal*[TIAB] OR "prospective study"[TIAB] OR "retrospective study"[TIAB]) AND Publication date 2000-2010 - English language only
    - Search Date: 14 August 2022

3. Pubmed: ("Tuberculosis"[Mesh] OR "Tuberculosis"[TI]) AND ("Alcohol Drinking"[Mesh] OR "Alcohol-Related Disorders"[Mesh] OR alcohol*[TIAB] OR drink*[TIAB]) AND ("Cohort Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Retrospective Studies"[Mesh] OR cohort[TIAB] OR longitudinal*[TIAB] OR "prospective study"[TIAB] OR "retrospective study"[TIAB]) AND 2022/05/30:2022/09[EDAT] AND Publication date 2000-2022-08-31 - English language only
    - Search Date: 31 August 2022

PREFERRED REPORTING ITEMS FOR SYSTEMATIC REVIEWS AND META-ANALYSES (PRISMA) FLOW DIAGRAM OF STUDY SELECTION



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